REMARKS

The pending claims (claims 1-22) remain directed to certain potassium channel inhibitors, compositions and related methods. Applicants note that claims 1-22 have been acted upon in the Detailed Action, notwithstanding the earlier restriction requirement. Note also that the rejection of claim 22 is not listed on the Office Action Summary. Applicants, remarks are directed to all of the rejections discussed in the Detailed Action.

Applicants note with appreciation the indication that claims 4, 10, 12 and 15-21 would allowable if rewritten in independent form. The Office Action acknowledges that the record prior art "do not teach compounds of formula (I) having R^2 as a substituted pyridyl ring." Applicants are confident that the remaining claims also will be found allowable and thus are not amending these claims at this time. Applicants also appreciate the indication in the Office Action that the prior response had overcome some of the earlier rejections under 36 USC 112, paras 1 and 2.

Claims 1-3, 5, 7-9, 11 and 13 and 14 have again been rejected under 35 U.S.C. 112, first paragraph. These rejections are respectfully traversed.

The Office Action initially contends that the specification lacks a written description for compounds where R^5 and R^6 form a ring, *i.e.*, a spiro cycle. According to the Office Action, "the specification does not have a description for the arrangement of atoms, especially when the ring is a heterocyclic spiro-cycle."

The application describes a generic class of R^5 and R^6 substituents using the language "R^5 and R^6 taken together, along with the carbon atom to which they are both attached, form a 3-membered to 7-membered carbocyclic, or heterocyclic ring." Applicants intend this description to be generic. The claims do not require a specific arrangement of atoms and thus a specific description of the arrangement of atoms in the specification is not required. Rather, the claims contain the same recitation that appears in the specification. In this context, that description is sufficient to satisfy the written description requirement. As an aside, applicants note that the specification does contain a description of heterocyclo in paragraph 69.

The Office Action next contends that the specification lacks enablement for the same claims with respect to compounds where R^5 and R^6 form a ring, *i.e.*, a spiro cycle, especially a heterocyclic one. According to the Office Action, "undue experimentation is required.

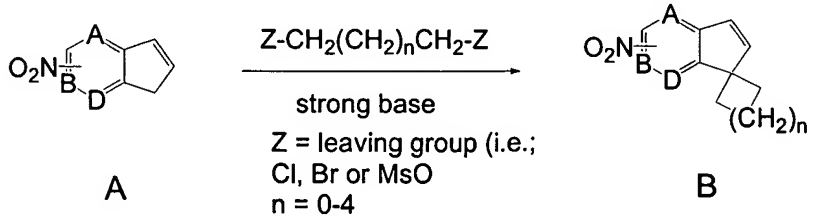
Section 112 requires that a specification provide a description which is enabling for a person skilled in the relevant art. The specification does not need to be directed to an unskilled individual. Indeed, a specification need not teach and preferably omits what is well known in an art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987). Here, the level of skill in the potassium channel inhibitor art is very high.

Indeed, specific (representative) working examples are not required to satisfy the enablement standard. *In re Robbins,* 429 F.2d 452, 166 USPQ 552 (CCPA 1970). All that is required is for the applicant to use some technique [such as showing representative reaction schemes] of providing a teaching of how to make and use the invention commensurate with the scope of protection sought **in view of the knowledge already available to skilled workers**. Here, even a cursory review of the specification illustrates that the general synthetic schemes bridging pages 26 through 30 of the application are presented in a way that illustrates the full scope of the claims. Given the high level of skill in this art, this is all that is required; specific examples of such syntheses are not required. When coupled with the skilled worker's general knowledge about making compounds with such structure, as described below, the application provides a sufficient enablement for this portion of the claims.

As noted in the prior response, preparation of compounds having a spiro structure is well within the skill in the art using techniques described in the literature well before the filing of the application on the present invention, for both carbocycles and heterocycles.

In particular, compounds of the present invention where R^5 and R^6 form a 3- to 7-membered carbocyclic ring may be prepared as described in the following Scheme 1, using a reaction technique several decades old and long understood by skilled workers.

Scheme 1

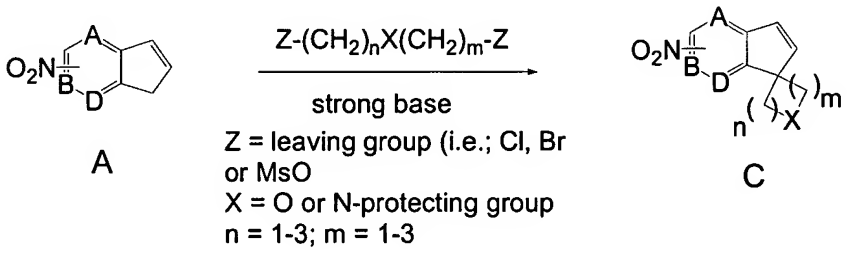


Indene compound A is prepared using procedures described in the application. Compound A then may be made to react with a compound of formula $Z\text{-}CH_2(CH_2)_nCH_2\text{-}Z$ where Z is a leaving group such as Br, Cl or OMs and n is an integer from 0 to 4 in the presence of a

strong base (i.e.; sodium hydride, sodium hydroxide, lithium bis(trimethylsilyl)amide or *n*-butyl lithium) in a solvent such as tetrahydrofuran or 1,2-dimethoxyethane or under phase transfer conditions to provide the spiro compound B. For example, 1*H*-Indene may be made to react with 1,2-dibromoethane in the presence of sodium hydride in 1,2-dimethoxyethane to provide the spiro cyclopropane derivative as described in *J. Amer. Chem. Soc.* **1972**, *94*, 4247-4255. 1*H*-Indene may be made to react 1,4-di-bromobutane under phase transfer conditions to provide the spiro cyclopentance derivative as described in *Tetrahedron Lett.* **1966**, 4621-4624. Thereafter, product B may be further manipulated as described in the application to provide compounds of the present invention. Such reactions are well within the skill of the art.

In a similar fashion, it also was well-within the skill of the art, at the time the subject application was filed, to prepare compounds of the present invention (US patent application No 10/004,867) where R^5 and R^6 form a heterocyclic ring. One art-recognized approach is illustrated in the following Scheme 2.

Scheme 2



Indene compound A, again prepared using procedures described in the application, may be made to react with a compound of formula Z-$(CH_2)_n$X$(CH_2)_m$-Z where Z is a leaving group such as Br, Cl or OMs, X is a heteroatom (i.e.; oxygen) or a protected heteroatom (i.e.; N-Boc or N-benzyl), n is an integer from 1 to 3 and m is an integer from 1 to 3 where the sum of n and m is less then or equal to 5 in the presence of a strong base (i.e.; sodium hydride, sodium hydroxide, lithium bis(trimethylsilyl)amide or *n*-butyl lithium) in a solvent such as tetrahydrofuran or 1,2-dimethoxyethane or under phase transfer conditions to provide the spiro product C. As with the technique of Scheme 1, this methodology has also been described in the literature before the filing of the subject application. For example, 1*H*-Indene may be made to react with bis-(2-chloro-ethyl)-carbamic acid tert-butyl ester in the presence of lithium

bis(trimethylsilyl)amide in tetrahydrofuran to provide the spiro piperidine derivative as described in *J. Med. Chem.* **1992**, *35*, 2033-2039. See also *J. Med. Chem.* **1994**, *37*, 2574-2582. 1*H*-Indene may be made to react with bis-(2-chloro-ethyl)ether or bis-(2-methanesulfonyloxy-ethyl)-ether in the presence of *n*-butyl lithium in hexane and/or tetrahydrofuran to provide the spiro tetrahydropyran derivative as described in *J. Chem. Soc. Dalton Trans.* **1998**, *10*, 1607-1612. Thereafter, product C may be further manipulated as described in the application to provide compounds of the present invention. As above, such techniques were within the synthesis arsenals of skilled workers prior to the filing of the present invention.

Claim 22 is now rejected under 35 U.S.C. 112, first paragraph, as failing to provide both an adequate written description and as lacking enablement for cell proliferative disorder. This rejetion is respectfully traversed.

The basis of the rejections apparently is that it is not understood what is meant by "cell proliferative disorder."

Those skilled in the art (the skill being very high in the context of potassium channel inhibition), recognize the term "cell proliferative disorder" as embracing a variety of conditions. In that regard, enclosed for consideration by the Examiner are U.S. Patents 5,808,007, 6,331,564 and 6,428,966 where this term finds specific use. Indeed, the Background section of the '564 patent, bridging columns 1-4, provides an informative discussion of such disorders. Based on this information, it is apparent that skilled workers understand what is meant by that phrase and more specificity is not required.

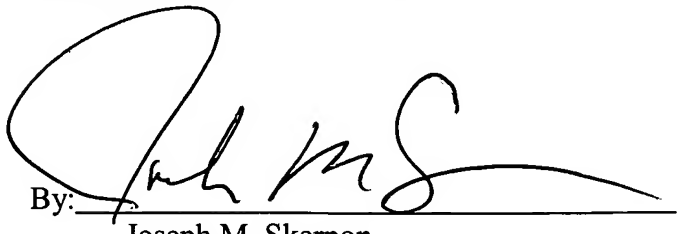
Applicants have shown that their compounds and thus the related compositions are potent inhibitors of potassium channel function. Thus, within the context of the present invention, where applicants have amended claim 22 to specify that the method is directed to **potassium channel mediated** cell proliferative disorders, and recognizing the high skill of the relevant audience, the application provides an adequate description and adequately enables the method of claim 22.

Therefore, when the teachings of the present invention are viewed from the perspective of the skilled worker, as such teachings are to be viewed, it is clear that skilled workers are able to practice the full scope of the pending claims. Applicants respectfully submit that claims are enabled, and request that the rejection of the claims under 35 U.S.C. §112, first paragraph be withdrawn.

On the basis of the foregoing, prompt reconsideration of claims 1-22 in the subject application is respectfully requested.

Respectfully submitted,

BANNER & WITCOFF, LTD.



Date: February 20, 2004

By: _____
Joseph M. Skerpon
Registration No. 29,864

1001 G Street, N.W.
Washington, D.C. 20001-4597
(202) 824-3000
JMS/bao